

SEPSIS SYNDROME IN UROLOGY (UROSEPSIS)

Background

- Urinary tract infections can manifest as bacteriuria (with limited clinical symptoms) sepsis or severe sepsis, depending on localised or systemic extension.
- **Sepsis** is diagnosed when **clinical evidence of infection is accompanied by signs of systemic inflammation (fever or hypothermia, tachycardia, tachypnoea, leukocyturia or leukopenia).**
- **Severe sepsis** is defined by the **presence of symptoms of organ dysfunction, and septic shock by the presence of persistent hypotension associated with tissue anoxia.**
 - mortality rate of 20-40%, men > women
 - Most severe sepsis: pulmonary (50%) abdominal (24%) **UTIs (5%).**
 - Globally (this is not true for urosepsis), the rate of sepsis due to fungal organisms has increased while G+ve bacteria is the predominant pathogen in sepsis (Gram-negative bacteria remain predominant in urosepsis).
- The severity depends mostly upon the host response. Patients who are more likely to develop urosepsis include:
 - **Elderly patients, Diabetics**
 - **Immunosuppressed patients:** such as transplant recipients patients receiving cancer chemotherapy or corticosteroids and patients with AIDS
- Urosepsis also depends on local factors, such as:
 - UT calculi, obst. at any level in the UT, cong. uropathy, neurogenic bl. disorders, or endoscopic manoeuvres.
 - SIRS may be present without inf. (e.g. pancreatitis, burns, or non-septic shock)

Definition and clinical manifestation of sepsis in urology

- The following definitions apply (Table 5.1):
- Sepsis is a **systemic response to Infection**. SIRS symptoms were considered mandatory for the diagnosis (now alerting symptoms).
 - Severe sepsis is **sepsis associated with organ dysfunction**.
 - Septic shock is persistence of hypoperfusion or hypotension despite fluid resuscitation.
 - Refractory septic shock is absence of response to therapy.

Table 5.1: Clinical diagnostic criteria of sepsis and septic shock (5,6)

Disorder	Definition
Infection	Presence of organisms in a normally sterile site that is usually, but not necessarily, accompanied by an inflammatory host response.
Bacteraemia	Bacteria present in blood as confirmed by culture. May be transient.
Systematic inflammatory response syndrome (SIRS)	Response to a wide variety of clinical insults, which can be infectious, as in sepsis but may be non-infectious in aetiology (e.g. burns, or pancreatitis). This systemic response is manifested by two or more of the following conditions: - Temperature > 38°C or < 36°C - Heart rate > 90 bpm - Respiratory rate > 20 breaths/min or PaCO ₂ < 32 mmHg (< 4.3 kPa) - WBC > 12,000 cells/mm ³ or < 4,000 cells/mm ³ or > 10% immature (band) forms
Sepsis	Activation of the inflammatory process due to infection.
Hypotension	Systolic blood pressure < 90 mmHg or a reduction of > 40 mmHg from baseline in the absence of other causes of hypotension.
Severe sepsis	Sepsis associated with organ dysfunction, hypoperfusion or hypotension. Hypoperfusion and perfusion abnormalities may include but are not limited to lactic acidosis, oliguria or acute alteration of mental status.
Septic shock	Sepsis with hypotension despite adequate fluid resuscitation along with the presence of perfusion abnormalities that may include, but are not limited to lactic acidosis, oliguria, or acute alteration in mental status. Patients who are on inotropic or vasopressor agents may not be hypotensive at the time that perfusion abnormalities are measured.
Refractory septic shock	Septic shock that lasts for > 1 h and does not respond to fluid administration or pharmacological intervention.

Physiology and biochemical markers

- Microorganisms reach the urinary tract by way of the ascending, haematogenous, or lymphatic routes.
- **For urosepsis, pathogens must reach bloodstream.**
- *E. coli* remains the most prevalent microorganism.
- Some microorganisms are multi-resistant, such as methicillin-resistant *Staphylococcus aureus* (MRSA), *P. aeruginosa* and *Serratia* sp. and therefore difficult to treat.

Cytokines as markers of the septic response

- Cytokines are involved in the pathogenesis of sepsis syndrome.
- They are peptides that regulate the amplitude and duration of the host inflammatory response.
- Released from various cells including monocytes, macrophages and endothelial cells, in response to various infectious stimuli.
- Bound to specific receptors on other cells
- **An immunosuppressive phase follows the initial pro-inflammatory mechanism.**
- Cytokines associated with sepsis
 - **Tumour necrosis factor (TNF)- α , IL-1, IL-6 and IL-8.**
- Genetic predisposition is a probable explanation of sepsis in several patients.

Procalcitonin is a potential marker of sepsis

- **Procalcitonin** is the propeptide of calcitonin
- levels are undetectable in healthy humans.
- During severe generalised infections (bacterial, parasitic and fungal) with systemic manifestations, procalcitonin levels may rise

to > 100 ng/mL. (not with severe viral infections or inflammatory reactions of non-infectious origin)

- useful in differentiating between infectious and non-infectious causes of severe inflammatory status.

Prevention

- Septic shock is the most frequent cause of death for patients hospitalised for community-acquired and nosocomial infection.
- Sepsis → severe sepsis → septic shock.
- Urosepsis treatment
 - treatment of the cause (obstruction of the urinary tract),
 - adequate life-supporting care, and
 - appropriate antibiotic therapy

Preventive measures (for nosocomial urosepsis as other nosocomial inf.):

- Isolation of all patients infected with multi-resistant organisms to avoid cross-Infection.
- Prudent use of antimicrobial agents for prophylaxis and treatment of established Infections, to avoid selection of resistant strain
- Reduction In hospital stay.
- Early removal of indwelling urethral catheters. Use of closed catheter drainage and minimization of tweaks In the Integrity of the system, e.g. for urine or bladder wash-out.
- Use of least-invasive methods to release urinary tract obstruction until the patient is stabilised.
- Attention to simple everyday techniques to assure asepsis, Including the routine use of protective disposable gloves, frequent hand disinfection, and using Infectious disease control measures to prevent cross-Infections.
- ***Appropriate perioperative antimicrobial prophylaxis***

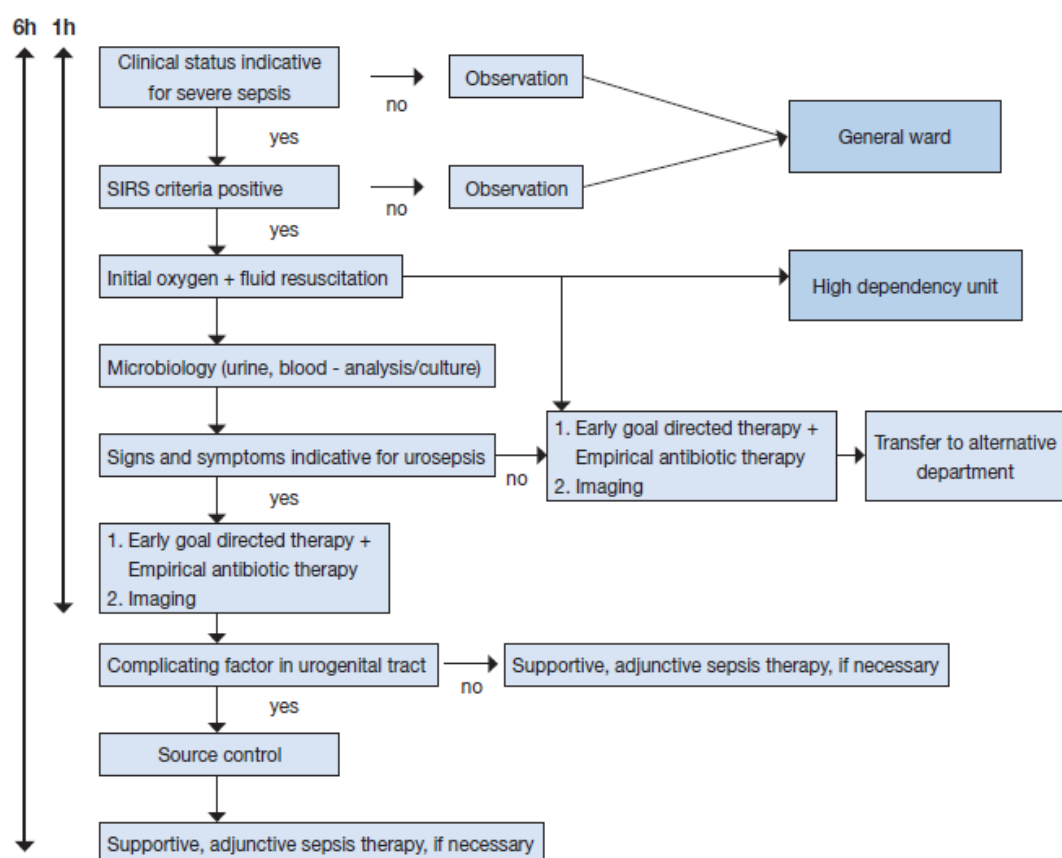
Preventive measures of debatable efficacy

- Instillation of antibiotic or antiseptic drugs into catheters and drainage bags.
- Use of urinary catheters coated with antibiotics or silver.

Ineffective or counterproductive measures

- Continuous or intermittent bladder irrigations with antibiotics or urinary antiseptics that increase risk of infection with resistant bact.
- Routine administration of antimicrobial drugs to catheterised patients → reduces the incidence of bacteriuria only for a few days and increases risk of infection with multi-resistant bacteria (reserved for immunosuppressed patients).

Figure 5.1: Clinical algorithm for the management of urosepsis



5.7 Treatment

5.7.1 Clinical algorithm for management of urosepsis

Table 5.2: Early goal directed therapy

Early goal directed therapy	
Central venous pressure (CVP)	8-12 mmHg
Mean arterial pressure (MAP)	65-90 mmHg
Central venous oxygen (CVO ₂)	≥ 70%
Haematocrit (HKT)	> 30 %
Urine output	> 40 mL/h

Table 5.3: Levels of therapy in sepsis

Levels of therapy in sepsis	
Causal therapy	1. Antimicrobial treatment 2. Source control
Supportive therapy	1. Haemodynamic stabilisation 2. Airways, respiration
Adjunctive therapy	1. Glucocorticosteroids 2. Intensified insulin therapy

Relief of obstruction

Drainage of any obstruction in the urinary tract and removal of foreign bodies, such as urinary catheters or stones, should lead to resolution of symptoms and recovery (**an absolute emergency**).

Antimicrobial therapy

Empirical initial treatment should provide broad antimicrobial coverage and should later be adapted on the basis of culture results.

- The dosage generally be high.
- not later than 1 h after clinical assumption of sepsis.

Adjunctive measures

The management of fluid and electrolyte balance is a crucial aspect of patient care in sepsis syndrome particularly if complicated by shock

- **Volaemic expansion and vasopressor therapy** is important to maintain adequate tissue perfusion and oxygen delivery, stabilisation of arterial pressure.
- **Hydrocortisone** (with a debate on dosage) is useful in patients with relative insufficiency in the pituitary gland-adrenal cortex axis (adrenocorticotropin test)
- Tight blood glucose control by administration of insulin doses up to 50 U/h is associated with a reduction in mortality.
- The use of human albumin and human recombinant activated protein C is debatable.

Conclusion

- Sepsis syndrome in urology is severe situation with a mortality rate (20-40%).
- ‘Surviving Sepsis Guidelines’, aimed to reduce mortality by 25%
- Early recognition of the symptoms may decrease the mortality by timely treatment of urinary tract disorders, e.g. obstruction, or urolithiasis.
- Adequate life-support measures and appropriate antibiotic treatment provide the best conditions for improving patient survival.

Summary and recommendations

- Patients with urosepsis should be diagnosed at an early stage, especially in the case of a complicated UTI.
- SIRS (fever or hypothermia, hyperleukocytosis or leukopenia, tachycardia, tachypnoea), is recognised as the first event in a cascade to multi-organ failure.
- Mortality is considerably increased when severe sepsis or septic shock are present, although the prognosis of urosepsis is globally better than that of sepsis from other infectious sites.
- **The treatment of urosepsis calls for the combination of**
 - **adequate life-supporting care,**
 - **appropriate and prompt antibiotic therapy,**
 - **adjunctive measures (e.g. sympathomimetic amines, hydrocortisone, blood glucose control) and the**
 - **optimal management of urinary tract disorders (drainage of any obstruction in the urinary tract is essential as first-line treatment**
 - **With help of ICU specialist**
- Urosepsis is seen in both community-acquired and healthcare associated infections.
- Most nosocomial urosepsis can be avoided by measures used to prevent nosocomial infection, e.g.
 - reduction of hospital stay,
 - early removal of indwelling urethral catheters,
 - avoidance of unnecessary urethral catheterisation,
 - correct use of closed catheter systems, and
 - attention to simple daily asepsis techniques to avoid cross-infection

Recurrent UTIs

Cause:

- 1) reinfection
 - usually different organisms with variable intervals
 - uncommon in M and are usually associated with GU tract abnormality
 - common in F and usually don't have correctable cause
- 2) bacterial persistence from nidus
 - same organism, short interval
 - generally uncommon

Management of recurrent UTIs:

- reinfections
 - urologic evaluation if RFs (DM, hematuria, stone hx, analgesic abuse, LUTS, pyelo, etc)
 - removal of any infectious focus
 - if no RFs but related to coitus
 - post-coital prophylaxis
 - if no RFs and unrelated to coitus
 - low-dose prophylaxis
 - self-start Rx
 - culture-directed Rx each time
- bacterial persistence
 - urologic evaluation } CT + cysto
 - removal of infectious focus
 - if recurrent symptoms + repeated -ve cultures then do full urologic evaluation to r/o other causes

- consider non-medical Rx options } high fluid intake, frequent voiding, treat constipation, cranberry juice, probiotics, estrogen replacement
- consider Dx of STD

What are the correctable causes of bacterial persistence?

→ recall, reinfection UTI more common than persistent/relapsing UTI

- Papillary necrosis - Ureteral stump (infected post Nx)
- Urachal cyst (infected) - Prostatitis (chronic bacterial)
- FB - MSK
- Fistulae (enterovesical, rectourethral, VVF) - Abscess (perivesical, perinephric)
- Ectopic ureter - Stones (infected) } **most common**
- Diverticulum (urethral) - Kidney (atrophic segment)

Diagnosis

- Recurrent UTIs are common among young, healthy women, even though they generally have anatomically and physiologically normal urinary tracts.
- Recurrent UTIs need to be diagnosed by urine culture.

Excretory urography, cystography and cystoscopy are not routinely recommended for evaluation of women with recurrent UTIs.

What are the common Abx of choice for low-dose prophylaxis:

- nitrofurantoin 50mg od - Keflex 250mg od
- Septra SS tab od - cipro 250mg od } only if above regimes fail or are not tolerated
- Trimethoprim 100mg od

What are the recommendations for self-directed Abx therapy:

- obtain urine C&S with initiation of symptoms
- start on 3day course } cipro, Septra DS, nitrofurantoin ideal

What is the role of cranberry juice in recurrent UTIs?

- contains proanthocyanidins that **block bacterial adherence to uroepithelium**
- Cranberry (*Vaccinium macrocarpon*) is useful in reducing the rate of lower UTIs in women.
- Daily minimum of 36 mg/day proanthocyanidin A (the active compound), is recommended
- The best approach is to use those compounds that have demonstrated clear bioactivity in urine.
- some studies show a significant decrease in symptomatic recurrent UTIs

Prevention

Different therapeutic options can be recommended to the patient.

Antimicrobial prophylaxis

- only after counselling and behavioural modification has been attempted.
- Before any prophylaxis regimen is initiated, eradication of a previous UTI should be confirmed by a negative urine culture 1-2 weeks after treatment.
- Continuous or postcoital antimicrobial prophylaxis should be considered to prevent recurrent uncomplicated cystitis in women in whom non-antimicrobial measures have been unsuccessful

Immunoactive prophylaxis

- **OM-89 (Uro-Vaxom®)** is sufficiently well-documented
- Therefore, it can be recommended for immunoprophylaxis in female patients with recurrent uncomplicated UTI
- Others:
 - o StroVac® and Solco-Urovac® have been shown to be effective when administered with a booster cycle of the same agents
 - o Others: Urostim® and Urvakol®, no controlled studies

3.5.2.3 Prophylaxis with probiotics

- Only the Lactobacillus strains specifically tested in studies should be used for prophylaxis.
- The use of intravaginal probiotics that contain L. rhamnosus GR-1 and L. reuteri RC-14 for the prevention of recurrent UTI (once or twice weekly).
- Daily use of the oral product with strains GR-1 and RC-14 can restore vaginal lactobacilli, compete with urogenital pathogens, and prevent bacterial vaginosis, which increases the risk of UTI.

List causes of unresolved bacteriuria (CHART)

- 1) **bacterial resistance to ABx (most common)**
- 2) development of resistance from initially susceptible bacteria → occurs in 5%
- 3) bacteriuria caused by 2 bacterial species with mutually exclusive susceptibilities
- 4) rapid infection with a new, resistant species during original therapy
- 5) renal failure (urine concentration too low)
- 6) papillary necrosis from analgesic abuse
- 7) giant staghorn stone
- 8) self-inflicted infections or deception (variant of Munchausen's)

What is the management of unresolved bacteriuria?

- presume resistance
- 7days of different Abx
- adjust to C&S results

Table 3.3: Continuous antimicrobial prophylaxis regimens for women with recurrent UTIs

Regimens	Expected UTIs per year
TMP-SMX* 40/200 mg once daily	0-0.2
TMP-SMX 40/200 mg thrice weekly	0.1
Trimethoprim 100 mg once daily	0-1.5**
Nitrofurantoin 50 mg once daily	0-0.6
Nitrofurantoin 100 mg once daily	0-0.7
Cefaclor 250 mg once daily	0.0
Cephalexin 125 mg once daily	0.1
Cephalexin 250 mg once daily	0.2
Norfloxacin 200 mg once daily	0.0
Ciprofloxacin 125 mg once daily	0.0
Fosfomycin 3 g every 10 days	0.14

*Trimethoprim-sulfamethoxazole

**high recurrence rates observed with trimethoprim use associated with trimethoprim resistance

Table 3.4: Postcoital antimicrobial prophylaxis regimens for women with recurrent UTIs (33)

Regimens	Expected UTIs per year
TMP-SMX* 40/200 mg	0.30
TMP-SMX 80/400 mg	0.00
Nitrofurantoin 50 or 100 mg	0.10
Cephalexin 250 mg	0.03
Ciprofloxacin 125 mg	0.00
Norfloxacin 200 mg	0.00
Ofloxacin 100 mg	0.06

*Trimethoprim-sulfamethoxazole